SAFE SCIENCE IS GOOD SCIENCE

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MANUSCRIPT RECEIVED 11 MAY, 2015; ACCEPTED 29 MAY, 2015

INTRODUCTION

Each year thousands of student researchers pursue honors theses and practicums at university laboratories in preparation for future careers. While many will learn the nuances of performing biomedical research, a majority will likely graduate without knowing much about biosafety. As a new generation of scientists emerge from academia, it is crucial that they learn about the value of biosafety and begin to develop safe work practices to protect themselves, others, and the environment. Researchers must practice laboratory techniques and safety skills with equal diligence. Individual responsibility is the foundation for developing a culture of safety in biomedical research.

WHAT IS BIOSAFETY?

Biosafety is a form of risk management. The ultimate goal of biosafety is to decrease the incidence of laboratory-associated infections (LAIs) by lowering the risk of accidental exposure to biological agents through a combination of risk assessment and mitigation strategies. There is never a total reduction in risk, but the probability of an undesired outcome can be reduced to almost zero with an appropriate understanding of the risks presented by the agent, the procedures involved in the research, and the facilities where the work is conducted.

The practice of biosafety has progressively become a mainstream discipline and an international profession in itself. Several national and international biosafety associations exist to enable biosafety professionals to share best practices, inform policy discussions, and provide guidance on standards. Biosafety professionals work in occupational health and safety programs at universities, corporations, nonprofits and government agencies. They perform risk assessments and establish controls on practice and procedures to protect the worker, public, and environment. Hazard analysis, applied research, engineering, program management, emergency response, microbiology, molecular biology, and even investigative work are common elements of the biosafety profession.

WHAT SHOULD BE CONSIDERED IN A RISK ASSESSMENT?

A risk assessment is a formal consideration of the potential hazards associated with a particular agent and its use. When conducting a biosafety risk assessment, one must be able to identify possible sources and routes of infection to the worker. Once the hazards are anticipated, specific controls can be put into place to reduce the risk of LAIs.

There are many factors that must be considered when conducting a standard risk assessment, but they can generally be categorized as either agent hazards or laboratory hazards. Agent hazards are the intrinsic or modified characteristics of a biologic that may have an adverse impact on health. The type of species or strain used, virulence, transmissibility, resistance, infectious dose, tropism, and other factors are crucial elements to consider when evaluating the inherent risk of an agent to cause disease. The potential outcomes of natural mutation and genetic engineering must also be considered when assessing the hazards of an agent. A determination as to whether a biological agent is harmful depends on the host as well. What may be a harmless microorganism to a healthy individual could be a formidable pathogen leading to disease in another individual who has a weakened immune system. For example, the yeast, *Candida albicans*, is an opportunistic pathogen commonly found in human flora. Individuals who are immunocompromised, such as those with autoimmune diseases or who undergo chemotherapy treatment may develop serious disease when infected with this organism.

The risk of an LAI also depends on laboratory hazards. Laboratory hazards are vulnerabilities in the lab environment that increase the risk of injury or illness. Unsafe practices such as recapping a syringe may lead to a sharps injury. Common practices like pipetting, vortexing, sonication, and other aerosol-generating procedures may create bioaerosols leading to a potential inhalation exposure. Faulty equipment such as a cracked seal in a centrifuge cup have been known to release aerosols. Among the most common of all laboratory hazards is the failure to wear the right attire and personal protective equipment (PPE) appropriate for the laboratory procedure to be performed.

Although risk assessment often involves considering many factors at the same time, its purpose is not to confound but to clarify. Its careful application reveals potential hazards and vulnerabilities before research begins. Preventive action can be taken to protect the worker and others. No matter how virulent or transmissible the microorganism, it cannot cause disease if proper biosafety measures are implemented to prevent exposure.

HOW IS RISK REDUCED?

Once the agent and laboratory hazards are assessed, steps must be taken to reduce the likelihood of potential harm to the worker. In the biosafety field, it is standard practice to categorize research with biological hazards according to a "biosafety level". Based on the risk assessment, work with a pathogen can be assigned to Biosafety Levels (BSL) 1 through 4, with BSL-4 offering the highest protection to the worker and the environment. Each biosafety level builds upon the safety requirements of the previous level. An appropriate combination of microbiological practices, safety equipment, personal protective equipment, and facility design according to each biosafety level reduces the risk of potential biological exposures.

An undergraduate microbiology teaching laboratory may be considered a BSL-1 laboratory. BSL-1 typically involves work with agents that are not known to cause disease in healthy adults. *Bacillus subtilis, Naegleria gruberi, Escherichia coli* (K12) are examples of agents that may be used in a BSL-1 laboratory. The protection afforded by BSL-2 practices and procedures should be utilized when working with moderate-risk agents that can be acquired through mucous membrane exposure, percutaneous injury or ingestion. Examples of agents that may be used in a BSL-2 laboratory include *Staphylococcus aureus, Pseudomonas aeruginosa*, and the measles virus. In the case of measles, BSL-2 is appropriate because adequate vaccines are available. Biosafety Level 3 (BSL-3) is assigned for potentially lethal agents that are known to be transmitted *via* aerosols and may or may not be indigenous to the region. *Mycobacterium tuberculosis*, highly pathogenic avian influenza A virus, and *Francisella tularensis* are a few common examples of agents worked with in BSL-3 laboratories. When there are no treatments available for life-threatening infectious diseases caused by exotic pathogens, and there is a high individual risk to the worker, particularly through the aerosol route, these agents are handled under BSL-4 conditions. These laboratories are usually referred to as maximum-containment facilities and provide the highest levels of protection for the laboratory worker. Ebola virus, Marburg virus, Crimean-Congo Hemorrhagic Fever virus and Nipah virus are examples of pathogens that require BSL-4 containment.

In addition to these standard biosafety levels, there are specific containment designations depending on the activity being performed. For example, infectious disease work involving animals are designated as Animal Biosafety Levels 1, 2, 3 and 4 (ABSL). The challenges presented by the animal model are taken into consideration when performing a risk assessment. Animals can be unpredictable. They can bite, scratch, kick, shed fluids, produce splashes and aerosols, and increase the risk of accidental exposure to the worker. Some animals may even be infected naturally with zoonotic agents that can cause dangerous, sometimes deadly infections. Research involving large or loose-housed animals is conducted in specially designed BSL-3-Agriculture (BSL-3 Ag) laboratories. In this scenario, the risk assessment places greater emphasis on preventing the pathogen from escaping into the environment. If there were a release of an agricultural pathogen, the economic implications could be significant. For example, an accidental release of a pathogen that infects cattle could potentially impact a $44 billion industry. A useful resource for learning more about biosafety levels is the CDC/NIH publication, *Biosafety in Microbiological and Biomedical Laboratories* 5th edition (4).

THE VALUE OF BIOSAFETY

Careful adherence to biosafety principles protects individuals, reputations, and research. Perhaps the best way to communicate the value of biosafety is through the tragic example of a laboratory-associated infection that occurred at Yerkes Regional Primate Center at Emory University. On October 29, 1997, a young researcher was conducting a routine procedure that involved moving a non-human primate in caging. The primate, a rhesus macaque (*Macaca mulatta*), was unknowingly infected with a zoologic virus known as *Macacine herpesvirus* (formerly *Cercopithecine herpesvirus* 1 [CHV-1]). The pathogen can be present in monkey saliva, urine, fecal matter, and conjunctival fluid. Although disease is usually mild in primates, it is frequently deadly in humans who are exposed to the virus. During the transfer, the researcher suffered an ocular exposure to hazardous macaque fluids. Despite having flushed her eyes and later seeking medical attention, it was not enough to save the worker's life. Just 42 days later, she died due to refractory respiratory failure from this seemingly minor exposure. A subsequent CDC/OSHA investigation found that the primate center believed the risk of CHV-1 exposure was thought to be low for the activity, that eye wash first aid was not conducted for at least 15 minutes, and that medical reporting and subsequent treatment was delayed. These factors contributed to a terrible outcome (1, 5).

Seemingly innocuous microorganisms can lead to serious LAIs as well. In 2009, an associate professor at the University of Chicago became the first person to die from an accidental exposure to an attenuated *Yersinia pestis* strain. The researcher worked with pigmentation-negative KIM D27, a strain considered avirulent because of its iron-acquiring limitations. However, host factors in the researcher appear to have made the laboratory strain virulent. Hemochromatosis is a hereditary medical condition in which the body absorbs too much iron and deposits excess amounts in organs. It is believed that after the researcher experienced a percutaneous or mucosal exposure in the laboratory, the KIM D27 strain was able to establish an infection due to elevated iron levels in his body. An investigation revealed that the researcher did not wear appropriate personal protective equipment and did not have current biosafety training. This case highlights the importance of consistently practicing biosafety recommendations to mitigate unknown risk factors (2).

It is clear that improper adherence to biosafety practices and resulting LAIs could have a devastating impact on the individual. However, it is worth taking a moment to appreciate the bigger picture: the impact unsafe practices in the laboratory could have on co-workers, the general public, the environment, and the overall research enterprise. Recently, the Centers for Disease Control and Prevention (CDC) has been in the news media about several incidents where biosafety protocols and procedures have been breached. Most notably, the unintentional exposure of personnel to potentially viable anthrax and the cross-contamination of non-pathogenic avian influenza virus with the highly pathogenic avian influenza virus strain H5N1. In both cases, the lack of proper adherence to biosafety protocols led to potential exposures outside the laboratory. As a result, research activities of the laboratories involved in this incident were suspended. Significant time and funding were spent to investigate the incidents, re-inspect inventories, and retrain personnel. One could argue that the most important loss in the ensuing months has been the public trust and confidence in the scientific enterprise to conduct biomedical research safely with high-risk pathogens (3, 6). How can this trust be regained? How can future incidents be prevented? Diligent adherence to biosafety practices and procedures while working in the laboratory will ensure that workers are safe, the community and environment is protected and the progress of vital scientific research is not interrupted.

HOW CAN STUDENTS CONTRIBUTE TO BIOSAFETY?

Students can protect themselves and others by taking laboratory safety seriously. They should expect their departments to provide safe work spaces and comprehensive laboratory training. Before beginning research, students should make sure their project has undergone a formal risk assessment and that they feel comfortable performing it safely. Students should learn how to safely operate any equipment before using it and always follow standard operating procedures. Personal protective equipment must always be worn. Know what to do and whom to contact when an accident occurs, such as a spill, injury, or illness. If students have safety questions or concerns, they should make them known to their faculty or institutional safety office. Student researchers may even consider contributing to applied biosafety research, for example, by studying potential routes of contamination in a laboratory using a harmless surrogate or by evaluating the effectiveness of the institutional biosafety program.

SUMMARY

Biosafety is a multi-faceted discipline, a form of risk management designed to minimize the risk of biological exposures and prevent laboratory-associated infections. Biosafety professionals protect the research community's health and safety by assessing research and setting risk reduction strategies. For these strategies to be successful, student researchers and faculty advisors must commit to incorporating them into their daily research activities. Those who understand the value of biosafety will not only protect themselves and others but will also advance research by realizing that safe science is good science.

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